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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/708,506	11/09/2000	Arno Hartmann	MERCK-2056	2626
22832	7590	06/02/2005	EXAMINER	
KIRKPATRICK & LOCKHART NICHOLSON GRAHAM LLP (FORMERLY KIRKPATRICK & LOCKHART LLP) 75 STATE STREET BOSTON, MA 02109-1808			DEBERRY, REGINA M	
			ART UNIT	PAPER NUMBER
			1647	

DATE MAILED: 06/02/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/708,506

Applicant(s)

HARTMANN ET AL.

Examiner

Regina M. DeBerry

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 28 March 2005.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 2-4, 16-18, 24, 25, 27-30, 32, 33 and 35-40 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 2-4, 16-18, 24, 25, 28-30, 32, 33, 35-39 is/are rejected.
- 7) ☒ Claim(s) 27 and 40 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 9/04, 4/05.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date: _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 28 March 2005 has been entered.

Status of Application, Amendments and/or Claims

The amendment filed 29 December 2004 has been entered in full. Claims 1, 5-15, 19-23, 26, 31, 34 are cancelled.

Claims 2-4, 16-18, 24, 25, 27-30, 32, 33, 35-40 are pending.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

The information disclosure statement(s) (IDS) filed 20 September 2004 and

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11 April 2005 were received and comply with the provisions of 37 CFR §§1.97 and 1.98.

They have been placed in the application file and the information referred to therein has been considered as to the merits.

Withdrawn Objections And/Or Rejections

The rejection to claims 30, 32 and 33 under 35 USC 112, first paragraph, as set forth at pages 2-5 of the previous Office Action 29 September 2004 is *withdrawn* in view of the amendment (29 December 2004).

The rejection to claims 2 and 3 under 35 USC 112, second paragraph, as set forth at page 5 of the previous Office Action 29 September 2004 is *withdrawn* in view of the amendment 29 December 2004.

The objection to claims 4, 16-18, 24, 25, 28, 29, 35-39, as set forth at page 6 of the previous Office Action 29 September 2004 is *withdrawn* in view of the amendment 29 December 2004.

New Issues Are Set Forth Below:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

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Claims 2-4, 16-18, 24, 25, 27-30, 32, 33, 35 and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sytkowski *et al.* WO 99/02709 (reference of record) in view of Cox, III, U.S. Patent 6,608,183 B1.

Sytkowski *et al.* teach a fusion protein comprising an Fc portion of an Ig molecule and human erythropoietin (EPO) portion, wherein the Fc portion is fused covalently via its C-terminus directly or indirectly to the EPO portion (page 3, lines 6-31; page 16, lines 31-33 and column 14, lines 21-32)(**applies to claim 30**). Sytkowski *et al.* teach that EPO fusion proteins comprising immunoglobulin polypeptide chains will have increased biological activity and increased *in vivo* half-life compared to wildtype (page 2, lines 10-30; page 4, lines 12-18; page 5, lines 5-10 and page 19, line 8-page 21, line 8). Exemplary EPO molecules include mutant EPO with increased biology (page 5, lines 1-15 and page 8, line 17-page 12, line 22)(**applies to claims 2-4**). Sytkowski *et al.* teach that the entire immunoglobulin heavy chain constant region can be fused to the EPO molecule (page 15, lines 14-15)(**applies to claim 16**). Sytkowski *et al.* teach the use of human Fc (page 23, line 20)(**applies to claims 17, 18**). Sytkowski *et al.* teach pharmaceutical compositions comprising the EPO fusion protein (page 21, lines 9-31) (**applies to claims 24, 25**). Sytkowski *et al.* teach wherein the Fc portion is mutated or truncated (page 5, lines 11-20 and page 13, line 22-page 14, line 31) (**applies to claim 35**). Sytkowski *et al.* teach linkers (page 17, lines 5-16) (**applies to claim 39**). Sytkowski *et al.* do not teach cytokine substitutions in EPO.

Cox teach III, U.S. Patent 6,608,183 B1 teaches human EPO cytokine variants wherein the amino acids have a cytokine substituted. Cox teaches cytokine

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substitutions at amino acid positions corresponding to Gln86, Trp88 and Glu89 (column 23, lines 15-42 and column 26, lines 27-51)(**applies to claims 32, 33**). Cox teaches that in wildtype EPO, cysteines are located in amino acids positions 29 and 33 (lines 51-57)(**applies to claim 28**).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the fusion protein comprising an Fc portion of an Ig molecule and human EPO as suggested by Sytkowski *et al.* with cytokine substitutions in EPO as suggested by Cox with a reasonable expectation of success. The motivation and expected success is provided by Sytkowski and Cox, in that Sytkowski demonstrates increased biological activity and half-life when EPO is fused with an immunoglobulin and Cox who demonstrates another means of increasing EPO activity by making specific cytokine substitutions.

Claim 29 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sytkowski *et al.* WO 99/02709 in view of Cox, III, U.S. Patent 6,608,183 B1 as applied to claims 28, 30, 32, 33, above, and further in view of Okasinski *et al.*, U.S. Patent 5,888,772 (reference of record).

The teachings of Sytkowski *et al.* and Cox are described above. None of the references teach a cytokine substitution at amino acid residue position 139 in EPO. Okasinski *et al.* teach that the substitution of cytokine for the arginine at position 139 of human EPO results in improved *in vivo* EPO activity (column 5, lines 1-9 and column 6, lines 19-22) (**applies to claim 29**).

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It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the fusion protein comprising an Fc portion of an Ig molecule and human EPO as suggested by Sytkowski *et al.* with cytokine substitutions in EPO as suggested by Cox and Okasinski *et al.* with a reasonable expectation of success. The motivation and expected success is provided by Sytkowski, Cox and Okasinski in that Sytkowski demonstrates increased biological activity and half-life when EPO is fused with an immunoglobulin and Cox and Okasinski who demonstrate another means of increasing EPO activity by making specific cytokine substitutions.

Claims 36-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sytkowski *et al.* WO 99/02709 in view of Cox, III, U.S. Patent 6,608,183 B1 as applied to claim 30 above, and further in view of Bolt *et al.*, U.S. 5,585,097.

The teachings of Sytkowski *et al.* and Cox are described above. None of the references teach mutations in Fc, wherein the asparagine at amino acid position 297 of IgG1 is mutated. Bolt *et al.*, U.S. 5,585,097 teach mutations wherein asparagine at position 297 in IgG1 is replaced with another amino acid that cannot be glycosylated (column 6, lines 28-54)(**applies to claims 36-38**).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the fusion protein comprising an Fc portion of an Ig molecule and human EPO as suggested by Sytkowski *et al.* with cytokine substitutions in EPO as suggested by Cox and Fc mutations in IgG1 as suggest by Bolt *et al.* with a reasonable expectation of success. The motivation and expected success is provided

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by Sytkowski and Cox, in that Sytkowski demonstrates increased biological activity and half-life when EPO is fused with an immunoglobulin and Cox who demonstrates another means of increasing EPO activity by making specific cytokine substitutions. Furthermore, altering the glycosylation of IgG1 at asparagine 297 would help the antibody avoid the complement dependent cytolysis pathway.

Claim Objections

Claims 27 and 40 are objected to for depending from a rejected claim.

Conclusion

No claims are allowed.

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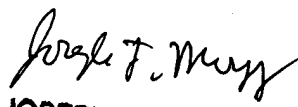
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (571) 272-0882. The examiner can normally be reached on 9:00 a.m.-6:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda G. Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



RMD
5/26/05


**JOSEPH MURPHY
PATENT EXAMINER**